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Supplemental Material

A Study of Reverse Causation: Examining the Associations of Perfluorooctanoic Acid Serum Levels with Two Outcomes

Radhika Dhingra, Andrea Winquist, Lyndsey A. Darrow, Mitchel Klein, and Kyle Steenland

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Calculation of yearly blood loss via menstruation

The expected accumulation of PFOA, when menstruation ends, can be estimated. We can assume a mean blood volume of 4.5 ± 1.1 L (Morgan et al. 2001), approximated from observed (mean \pm SD) weight at age 40 (152 ± 37 lbs.) in our cohort. Assuming a normal blood loss volume of 35–50 ml (Warrilow et al. 2004) per cycle, menstruation results in yearly blood loss (13 cycles) of ~ 455 -650 ml/year (10-14% of blood volume), though an alternative calculation estimates greater loss of PFOA by considering the non-blood fraction of menstrual fluid (Verner and Longnecker 2015). Given that PFOA is largely bound by albumin in serum (Post et al. 2012), the later calculation includes additional loss of PFOA under the assumption (according to their commentary, substantiated in Cederholm-Williams et al. 1984) that the non-blood portion of menstrual blood contains the same concentration of albumin that is contained in blood portion of menstrual fluid.

Brief summary of longitudinal reconstruction of modeled serum PFOA

Using mathematical modeling, historic serum PFOA concentrations were reconstructed for community participants using (1) an environmental fate and transport model to determine water source concentrations through time, (2) historical reconstruction of each individual's exposure, through air and water, based on residential history and reported water source, and (3) a single-compartment, toxicokinetic model for each individual (Shin et al. 2011a, 2011b).

For DuPont workers in the C8SP cohort (11.5%), job and department-specific occupational exposures were estimated based on $\sim 2,000$ historical serum PFOA measurements and participant work history (Woskie et al. 2012). All model estimation was done independently of PFOA values measured in 2005/06. Concurrent (i.e., modeled in the year of blood sampling) serum PFOA estimates have a Spearman correlation with serum PFOA concentrations measured in the blood sample (2005/06) of 0.71 (Winqvist et al. 2013).

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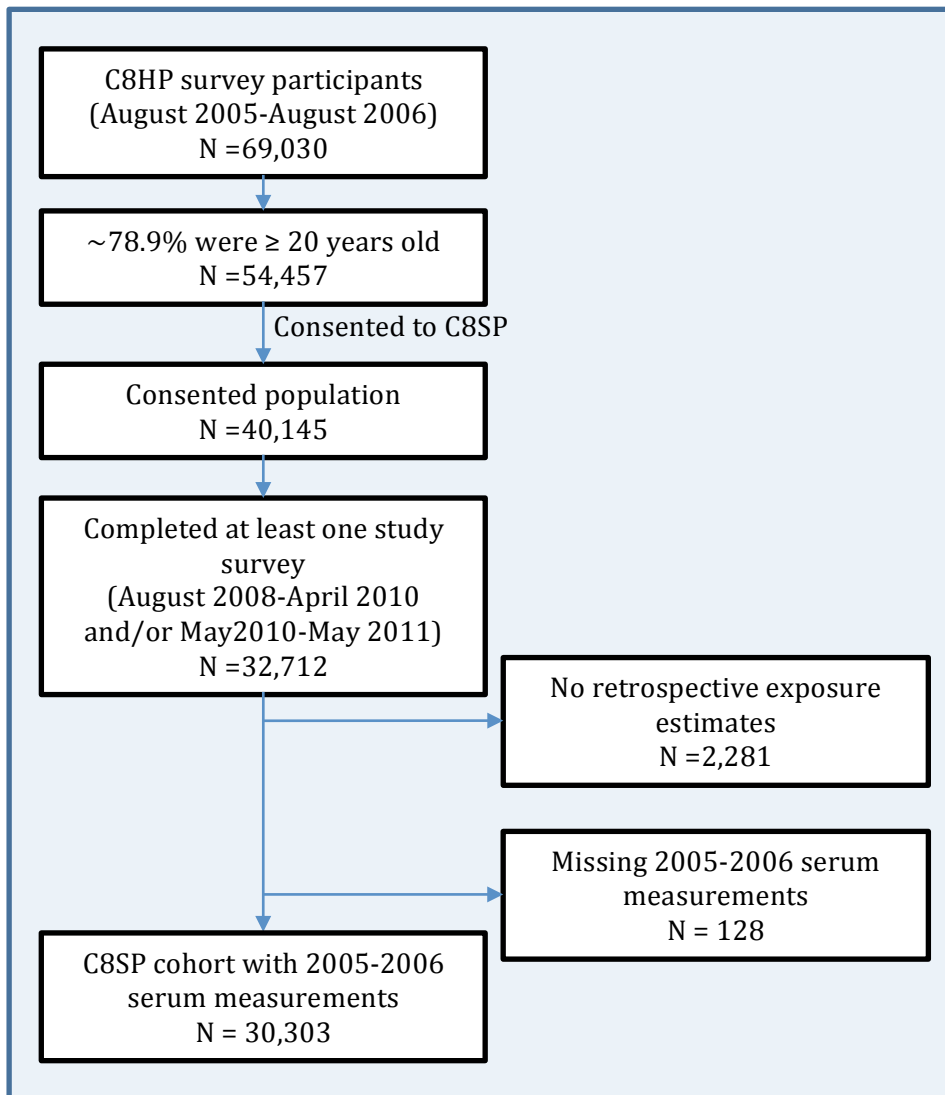


Figure S1. C8SP cohort with 2005-2006 PFOA serum measurements and estimates.

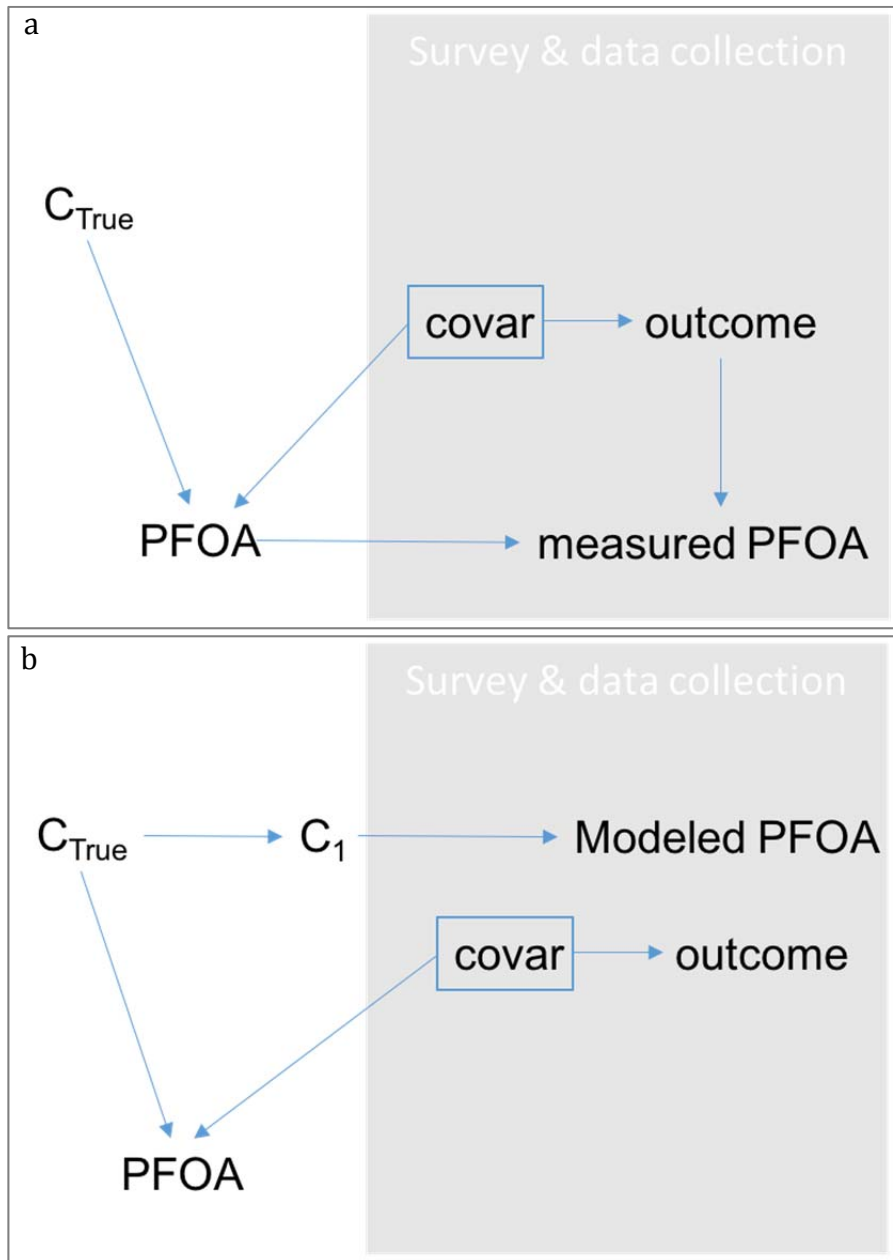


Figure S2. Causal diagrams showing the hypothesized relationship of (a) measured and (b) modeled PFOA to either outcome. C_{True} = True predictors of serum PFOA (e.g. residence, water ingestion, biological half-life); C_1 = modeling assumptions (e.g., reported residence, constant ingestion rate, assumed biological half-life); PFOA = refers to the etiologically relevant exposure of PFOA occurring before data collection; modeled PFOA = modeled serum PFOA at the time of data collection; measured PFOA = Serum PFOA measured in blood at the time of data collection; Outcome = menopausal status or kidney function as measured by eGFR; covar = potential confounders of the relationship between PFOA and outcome. Nodes contained in the grey box are observed and included in either our logistic models of menopause or continuous models of eGFR.

Table S1. Cohort characteristics of eGFR analyses (N=29,641).

GENDER		
	Female	55.6%
	Male	44.4%
HYPERTENSION		
	No	66.3%
	Yes	33.7%
HIGH CHOLESTEROL		
	No	76.5%
	Yes	23.5%
SMOKING		
	Never	47.4%
	Former	27.4%
	Current	25.2%
EDUCATION		
	Less than HS education	8.8%
	HS diploma	38.2%
	Some undergraduate	34.8%
	Bachelor's degree	18.3%
BMI		
	BMI≤18.5	1.4%
	18.5<BMI≤25	26.6%
	25< BMI≤30	34.9%
	BMI>30	37.2%
AGE AT BLOOD SAMPLING, 2005/2006		
	Mean (SD)	48.2 (15.2)
	Median	48.0
MEASURED SERUM PFOA, 2005/2006 (µg/mL)		
	Mean (SD)	87.0 (281.3)
	Median	26.1
MODELED SERUM PFOA, 2005/06 (µg /mL)		
	Mean (SD)	85.2 (189.7)
	Median	16.5
eGFR (mL/min/1.73m²)		
	Mean (SD)	77.1 (16.8)
	Median	76.3

Table S2. Cohort characteristics for menopause logistic regression (N=6,342) and 'years since menopause' (N=9,192) analyses.

	Logistic regression analysis	Years since menopause analysis		Logistic regression analysis	Years since menopause analysis
EDUCATION			BMI		
Less than HS education	5.40%	6.40%	BMI<18.5	1.40%	1.20%
HS diploma	33.80%	35.90%	18.5≤BMI<25	33.10%	31.40%
Some undergraduate	38.70%	38.90%	25≤BMI<30	28.70%	29.30%
Bachelor's degree	22.10%	18.90%	BMI≥30	36.80%	39.10%
PAROUS/NULLIPAROUS			SMOKING		
Nulliparous	11.20%	10.00%	Never	55.00%	54.60%
Parous	88.80%	90.00%	Current	24.50%	24.30%
DIABETES			Former	20.60%	21.10%
No	91.00%	89.20%	GROWS OWN VEGETABLES		
Yes	9.00%	10.80%	No	73.10%	73.40%
HIGH CHOLESTEROL			Yes	26.90%	26.70%
No	82.70%	84.90%	DRINKS BOTTLED WATER		
Yes	17.30%	15.10%	No	93.50%	94.30%
AGE CATEGORY IN 2005/2006			Yes	6.50%	5.70%
30 to 34	11.9	16.4	MONTHS OF BLOOD DRAW DURING SURVEY PERIOD		
35 to 39	13.8	17.2	First 2 months	10.90%	11.80%
40 to 44	14.5	15.8	Second 2 months	14.10%	14.80%
45 to 49	15.2	13.8	Third 2 months	26.80%	26.40%
50 to 54	15.9	14.2	Fourth 2 months	25.70%	25.70%
55 to 59	14.9	12.2	Fifth 2 months	13.60%	13.10%
60 to 65	13.9	10.4	Sixth 2 months	8.80%	8.20%
CURRENT WATER SOURCE			HAVING PREVIOUSLY LIVED/WORKED IN A CONTAMINATED WATER DISTRICT		
City of Belpre, OH	7.10%	7.50%	City of Belpre, OH	13.50%	13.40%
Tuppers Plains	13.50%	13.60%	Tuppers Plains	19.40%	19.40%
Little Hocking Water Association	13.00%	13.00%	Little Hocking Water Association	20.40%	19.80%
Lubeck Public Service District	10.80%	11.00%	Lubeck Public Service District	22.10%	22.00%
Mason County	14.80%	15.40%	Mason County	18.60%	19.20%
Village of Pomeroy	1.60%	1.90%	Village of Pomeroy	5.90%	6.10%
Well	4.50%	4.30%	Tested well	0.10%	0.10%
Study area, no qualifying source	34.70%	33.40%	MENOPAUSAL STATUS (2005/06)		
DUPONT WORKER			Still menstruating	62.90%	43.40%
No	97.70%	97.60%	Natural menopause	37.10%	25.60%
Yes	2.30%	2.40%	Hysterectomy	31.00%	-
MODELED SERUM PFOA (µg/mL), 2005/06			MEASURED SERUM PFOA (µg/mL), 2005/06		
Mean (Std. Dev.)	81.8 (175.0)	84.8 (179.7)	Mean (Std. Dev.)	69.2 (195.6)	74.6 (215.6)
Median	16.3	16.7	Median	21.4	23